Mathematical analysis of drug diffusion under anomalous environment and applications

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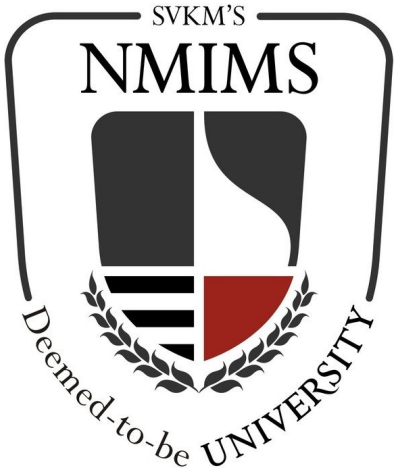

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Abstract

Chapter 1:

Some basic facts of the Caputo derivative, Riemann-Liouville fractional integral, fractional differential equations and Mittag-Leffler function are illustrated. Background of various concepts of special functions, anomalous drug diffusion, ADME process in pharmacokinetics is given.

Chapter 2:

Fractional Differential Equation (FDE) was used for diffusion-related processes. Fractional calculus was introduced through one-compartment pharmacokinetics and further extented for multi-compartmental drug diffusion models. Two and three-compartment models are evaluated and analyzed through different analytic and numerical methods. Theorems based on stability, existence, and uniqueness of the solutions for commensurate and non-commensurate linear and nonlinear FDE were demonstrated in the earlier study.

Chapter 3:

In the current study, drug level in the human body is studied using mathematical modelling, where the difference equations have been used as a means of analyzing the dosage over a prescribed time, reduction in dose half-life, and the total amount of residual drug in the blood-stream for a given time-period. Further, the differential equations approach is investigated for data fitting using Mathematica to extend the application adhering to the continuous nature of the inherent function. The perspective helps to preserve critical resources and render comparative results. In this approach, zero-order, first-order, and fractional order kinetics are explored and compared.

Chapter 4:

The present study explores multi-compartment FDE models with modified conditions for pharmacokinetics of anomalous drug diffusion in Caputo derivative sense. The Adomian decomposition method is implemented for analysis of non-commensurate model to depict the concentration of a single dose of enteric coated drug, in particular, Diclofenac in the blood plasma in two-compartment. Nonlinear regression is used for parameter estimation. In the present text, authors validated the model showcasing the best-fit for the experimental in-vivo data from the existing literature to ensure eradication of toxicity and ineffective treatment risk. Statistical analysis is performed using Mathematica to understand significance of each estimated parameter in the regression model. Stability analysis in graphical sense is examined for decision making. The authors have justified existence and uniqueness by Picard-Lindelöf theorem.

Chapter 5:

In the present study, ADME process is modelled by nonlinear compartmental fractional differential system. The existence and uniqueness of the proposed models are discussed. The models are evaluated using the fde12 algorithm on MATLAB, where in a code is generated for minimization of mean squared error (MSE) to estimate the parameters considered in the models via nonlinear regression (optimization algorithm) PSO. The experimental data-sets of Diclofenac delayed release and the drug concentration based on the stated model, motivated the authors to the present study. A comparitive study based on the suggested models are demonstrated in the context of MSE. The comprehensive results and evaluations are demonstrated through statistical analysis.

Chapter 6:

This paper presents a thorough validation of the proposed models designed to interpret anomalous drug diffusion in pharmacological compositions identified by extended or delayed release concentrations. The paper targets the growing demand for realistic

predictive models in drug delivery devices that display non-Fickian diffusion patterns in pharmaceutical research. The proposed models estimate key parameters influencing drug diffusion such as transfer rate, elimination rate and metabolism rate for several anomalous drugs giving good-fit with the experimental data from literature. Graphs have been plotted for time-concentration profile of considered drugs with suited models. Further, statistical analysis is done indicating robustness of the nonlinear models. By employing the rigorous mathematical models, the model seeks to represent the complex dynamics related to drug release profiles across time.

Chapter 7:

In the view of heterogeneity in the human body, in the current text, four compartmental FDE is considered to evaluate pharmacokinetics of F-choline in different compartments such as blood stream, liver, kidney and other tissues and organs. The proposed model is analysed for existence, uniqueness and stability. The parameters are estimated using MATLAB for the fit with data-set of prostatic cancer patients. The obtained graphs are compared with the results of ODE, stating the effectiveness of FDE. Further the statistical analysis is performed to validate the obtained results from the proposed model.

Chapter 8:

This study aimed to develop and evaluate regression models for predicting drug concentration in anomalous environments. Using a data-set of several drugs, we estimated the parameters of nonlinear fractional regression models, including metabolic parameter. The models were evaluated using analytic and numerical methods using MATLAB. The results showed that nonlinear fractional model with metabolic and elimination parameters achieved the highest accuracy in predicting drug concentration, with MSE value.

Chapter 9:

In the field of PKPD, categorized study between different age groups, gender and races can be motivated to observe the effect of drug and comparative study can be done

considering ADME rates in drug diffusion. Further, models can be presented for simulating interaction between drugs taken simultaneously. A code can be designed to evaluate non-commensurate FDE with parameters and also, to estimate the considered parameters. Fractional calculus can be utilized in the field of monitoring and predicting growth of tumor or cancer cells.

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CHAPTER 1

Introduction

1.1 Introduction

Diffusion is a fundamental mechanism underlying various processes in living organisms, including the distribution of drug within the body. Traditionally, diffusion is described by Fick's law, which assumes that a molecule undergoes a random walk, with its mean squared displacement proportional to time. However, over the past few decades, substantial experimental evidence has revealed that this classical view does not always hold true. In some cases, diffusion processes deviate from this norm, exhibiting either faster (super-diffusion) or slower (sub-diffusion) behaviors, where the mean square displacement follows a power law of time with an exponent greater than or less than 1, respectively. Such deviations from the classical model are termed anomalous diffusion, reflecting their departure from the expected behavior.

To explain these anomalous kinetics, one approach is fractal kinetics, which uses time-dependent coefficients in the form of explicit power functions of time to account for memory effects. Alternate approach employs fractional calculus, a mathematical framework that involves derivatives and integrals of non-integer (fractional) order. Although fractional calculus was first introduced by Leibniz over 300 years ago, its real-world applications have only been actively explored in recent decades. It has been demonstrated that differential equations incorporating fractional derivatives can more accurately describe experimental data related to anomalous diffusion. In this work, we aim to introduce these concepts into the pharmaceutical literature, showcasing

applications in drug dissolution and pharmacokinetics.

1.2 Definitions

In [1], authors defined Caputo's fractional derivative as:

$$ {}_{a}^{C}D_{t}^{\alpha}\phi\left(t\right)=\frac{1}{\Gamma\left(\alpha-n\right)}\int_{a}^{t}\frac{\phi^{(n)}\left(\xi\right)}{\left(t-\xi\right)^{\alpha-n+1}}d\xi \tag{1.1} $$

for $n-1<\alpha<n$, where α is an order of the fractional derivative, $n\in\mathbb{N}$ and a is the lower limit of t.

Linearity property of Caputo derivative [1] is given as:

$$ {}_{a}^{C}D_{t}^{\alpha}\left(p\phi\left(t\right)+q\varphi\left(t\right)\right)=p{}_{a}^{C}D_{t}^{\alpha}\left(\phi\left(t\right)\right)+q{}_{a}^{C}D_{t}^{\alpha}\left(\varphi\left(t\right)\right) \tag{1.2} $$

where p and q are arbitrary constants, $\phi\left(t\right)$ and $\varphi\left(t\right)$ are continuous functions.

Riemann-Liouville left-sided fractional integral of order $\alpha>0$ of a function $\phi(t)$ is given from [2] as:

$$ I^{\alpha}\phi\left(t\right)=\frac{1}{\Gamma\left(\alpha\right)}\int_{0}^{t}\frac{\phi\left(\xi\right)}{\left(t-\xi\right)^{1-\alpha}}d\xi;\ \alpha>0,\ t>0. \tag{1.3} $$

$$ I^{0}\phi\left(t\right)=\phi\left(t\right);\ \ \alpha=0. \tag{1.4} $$

Also from [1] and [2], we get:

$$ I^{\alpha}t^{\upsilon}=\frac{\Gamma\left(\upsilon+1\right)}{\Gamma\left(\upsilon+\alpha+1\right)}t^{\upsilon+\alpha};\ \alpha>0,\upsilon>-1,\ t>0. \tag{1.5} $$

In [1], Mittag-Leffler function for one parameter is defined by:

$$ E_{\alpha}\left(z\right)=\sum_{k=0}^{\infty}\frac{z^{k}}{\Gamma\left(\alpha k+1\right)};\ \alpha>0. \tag{1.6} $$

Mittag-Leffler function for two parameters is specified as:

$$ E_{\alpha,\beta}\left(z\right)=\sum_{k=0}^{\infty}\frac{z^{k}}{\Gamma\left(\alpha k+\beta\right)};\ \alpha,\beta>0. \tag{1.7} $$

1.3 Objective of the work

The objectives of this study are as follows:

1. To interpret the effect of metabolism parameter for appropriate drugs in ADME modeling.
2. To employ nonlinear variables in FDE models to simulate drug diffusion in pharmacokinetics.
3. To analyze the proposed models for the existence, uniqueness, and stability.
4. To validate the presented models through in-vivo drug dissolution experimental data-sets of various drugs from literature, which will provide a comprehensive validation of the model's predictive capabilities in real-life drug dissolution scenarios.
5. To execute parameter significance and normality of residuals through statistical analysis, which will impart a quantitative validation of the model's performance and reliability.

1.4 Scope of the thesis

The scope of the thesis was limited to:

1. Contribution of analytic solution of two and three-compartmental linear models in a closed form.
2. Proposing and evaluating mathematical models of drug diffusion with nonlinear variables and a metabolism parameter.
3. Presenting a MATLAB code to evaluate linear and nonlinear multi-compartmental fractional models and estimate the model parameters by minimizing Mean Squared Error.

4. Developing theory to test the existence, uniqueness, and stability of solutions of proposed models.

5. Investigating the validity of Mathematical models with drug dissolution experiments and data-sets of in-vivo clinical tests of various drugs.

6. Analyzing the significance of the parameters considered in the models through hypothesis testing and discussing the implications of the results on the validity and applicability of the models.

7. Application of fractional calculus to detect F-choline activity in PET scan for prostate cancer in various body organs.

CHAPTER 2

Literature Review

Leibniz and L′Höspital introduced the notion of differentiation for non-integer orders in 1695. Authors in [3] found that Fractional Differential Equation (FDE) is used for diffusion-related processes. Mainly in the compartmental study of drug diffusion, the transition rate is considered to be proportional to the contents of that compartment [4]. Instead, these conversion rates are expected to be proportional to complex functions of insertions of the compartment and time [5]. Authors of [6] introduced fractional calculus through one-compartment pharmacokinetics and drug dissolution applications. For the diffusion process which demonstrates characteristics of the memory effect, fractional calculus is recommended as an expedient tool for multi-compartmental modelling [7]. In [8], identifying and examining the differences between commensurate and non-commensurate models helped in the advancement of the theory of FDE in PK. As biological processes are modelled appropriately using nonlinear functions over linear models, authors in [9] explored a nonlinear function in the fractional two-compartmental model for improving the fit. Authors of [10], [11] and [12] analyzed two and three-compartment models with different analytic and numerical methods.

Authors in [13], [14] and [15] described the theorems based on stability, existence, and uniqueness of the solutions for commensurate and non-commensurate linear and nonlinear FDE. Adomian decomposition method has been applied to evaluate system of fractional differential equations by [16] successfully. The convergence of the solutions for FDE system is presented by [17]. In [18] and [19] the authors have

provided an algorithm namely; predictor-corrector method of Adams-Bashforth-Moulton for the numerical solution of nonlinear FDE which has been extended to multi-term FDE in 2003 for investigating mathematical models. For the said algorithm, [13] addressed an extensive error analysis and its convergence. Author in [20] elaborated linear stability analysis of an algorithm, which was previously presented by researchers in [18] and [19], further [20] developed routine fde12 in MATLAB.

CHAPTER 3

Drug Level Modelling with Difference and Differential Equations

Covid-19 drug level modelling through diffrence equation:

$$a_t = \begin{cases} r^t * 1800 & ; \quad 0 \leq t < 12 \\ r^t \left[1000 \left(1 + \dfrac{1}{r^{12}} \right) + 800 \left(\dfrac{1 - r^{-(t_1+12)}}{1 - r^{-12}} \right) \right] & ; \quad t_1 \leq t < t_1 + 12 \\ r^t \left[1000 \left(1 + \dfrac{1}{r^{12}} \right) + 800 \left(\dfrac{1 - r^{-336}}{1 - r^{-12}} \right) \right] & ; \quad t \geq 336 \end{cases} \tag{3.1}$$

for $t_1 = 12k,$ where $1 \leq k < 28.$

Some diffusional processes do not follow Fick's law. Super-division and sub-division are observed to follow mean-square displacement as non-integer power of time. The fractional calculus approach suits best describe such processes. Classical calculus is a special case of fractional calculus for $\alpha = 1$.

FDE for one-compartment is:

$$D^{\alpha} C_1 = -kC_1 \tag{3.2}$$

with the initial condition

$$C_1 \left(t_l \right) = l. \tag{3.3}$$

The solution for (3.2) is given by:

$$C_1 = lE_{\alpha} \left(-k(t - t_l)^{\alpha} \right). \tag{3.4}$$

CHAPTER 4

Analysis of Non-commensurate Model of Diclofenac Concentration in the Plasma to Enhance Drug Delivery System

Two-compartments can be expressed by the system of FDE (4.1) and (4.2),

$$\begin{aligned} D^{\alpha}C_1 &= -k_{21}C_1 \\ D^{\alpha}C_2 &= k_{21}C_1 - k_{02}C_2 \end{aligned} \tag{4.1}$$

with the initial conditions

$$C_1\left(t_l\right) = l, C_2\left(t_l\right) = 0. \tag{4.2}$$

The closed form of solution for C_1 as (3.4) and for C_2 by Adomian decomposition method can be represented as:

$$C_2 = \frac{k_{21}l}{k_{21} - k_{02}}\left[E_{\alpha}\left(-k_{02}(t-t_l)^{\alpha}\right) - E_{\alpha}\left(-k_{21}(t-t_l)^{\alpha}\right)\right] \tag{4.3}$$

provides the instantaneous estimate of drug concentration in second compartment (C_2) through solution of the compartmental model.

Three-compartment FDE is given as:

$$\begin{aligned} D^{\alpha}C_1 &= -k_{21}C_1 \\ D^{\alpha}C_2 &= k_{21}C_1 - k_{32}C_2 \\ D^{\alpha}C_3 &= k_{32}C_2 - k_{03}C_3 \end{aligned} \tag{4.4}$$

with the initial conditions

$$C_1\left(0\right) = l,\ \ C_2\left(0\right) = 0,\ C_3\left(0\right) = 0. \tag{4.5}$$

Solved using ADM as:

$$C_3 = k_{21}k_{32}l \left(\begin{array}{l} \dfrac{1}{k_{32}-k_{21}} E_\alpha\left(-k_{21}t^\alpha\right) \\ + \dfrac{1}{\left(k_{32}-k_{21}\right)\left(k_{32}-k_{03}\right)} E_\alpha\left(-k_{32}t^\alpha\right) \\ + \dfrac{1}{\left(k_{03}-k_{21}\right)\left(k_{03}-k_{32}\right)} E_\alpha\left(-k_{03}t^\alpha\right) \end{array} \right). \tag{4.6}$$

Two and three-compartmental models representing anomalous drug diffusion have been evaluated with the ADM analytic method, giving the closed form of the solutions. The two-compartment model is further analyzed for the solution's existence, uniqueness, and stability. The model is simulated for the concentration prediction of Diclofenac with the built-in function 'NonlinearModelFit', and statistical model analysis is done using the 'ParameterTable' function in Mathematica 13.

CHAPTER 5

Nonlinear Models: Analysis of Anomalous Drug Diffusion

FDE system with the initial conditions for drug diffusion is considered for $k = 0, 1, 2, \cdots, [\alpha]$ as follows:

$$D^{\alpha}\left[\mathbf{y}\left(t\right)\right] = \phi\left(t, \mathbf{y}\left(t\right)\right);\ \mathbf{y}^{(k)}\left(t_l\right) = \mathbf{c}_k \tag{5.1}$$

where $\phi\left(t, \mathbf{y}\left(t\right)\right) : [t_l, \tau] \times V \rightarrow \mathbb{R}^2$.
Considering $V_1 = \left[y_1\left(t_l\right) - r_1, y_1\left(t_l\right) + r_1\right]$ and $V_2 = \left[y_2\left(t_l\right) - r_2, y_2\left(t_l\right) + r_2\right]$ such that $V = V_1 \times V_2 \subset \mathbb{R}^2;\ t \in [t_l, \tau];\ \tau > t_l > 0;\ r_1, r_2 > 0$ and $0 < \alpha < 1$.
In the present study, two-compartmental models with $\phi\left(t, \mathbf{y}\left(t\right)\right)$ are proposed as:

$$\phi(t, \mathbf{y}\left(t\right)) = \left(\phi_1(t, \mathbf{y}\left(t\right)),\ \phi_2(t, \mathbf{y}\left(t\right))\right). \tag{5.2}$$

In (5.2), the function $\phi_1(t, \mathbf{y}\left(t\right))$ and $\phi_2(t, \mathbf{y}\left(t\right))$ are defined as:

$$\phi_1(t, \mathbf{y}\left(t\right)) = -k_{21} f_{1,d}\left(y_1\left(t\right)\right). \tag{5.3}$$

$$\phi_2(t, \mathbf{y}\left(t\right)) = k_{21} f_{1,d}\left(y_1\left(t\right)\right) - k_{02} y_2\left(t\right) - K_{02} f_2\left(y_2\left(t\right)\right). \tag{5.4}$$

The nonlinear functions $f_{1,d}\left(y_1\left(t\right)\right)$ and $f_2\left(y_2\left(t\right)\right)$ mentioned in equations (5.3) and (5.4) are defined as:

$$f_{1,d}\left(y_1\left(t\right)\right) = \frac{1 - e^{-\frac{y_1(t)}{l}}}{d} \tag{5.5}$$

and

$$f_2\left(y_2\left(t\right)\right) = \frac{y_2\left(t\right)}{K_m + y_2\left(t\right)} \tag{5.6}$$

where $\mathbf{y}(t) = (y_1(t), y_2(t)) \in \mathbb{R}^2$.

The two-compartmental nonlinear models with a metabolic parameter have been proposed, analyzed, and evaluated numerically using the presented MATLAB code. The models are simulated with an experimental data-set from [21], and comparison is demonstrated based on MSE. Estimated parameters are tested for significance by setting up the statistical hypothesis. Also, the prediction ability of the models is tested using a t-test on residuals.

CHAPTER 6

Validating the Proposed Models for Anomalous Drug Diffusion in Delayed Release Concentrations

In the study, the analysis of the nonlinear function given by (5.3) and (5.4) in two-compartmental models with the application in evaluating the pharmacokinetics of various delayed release drugs have been contributed,

where $f_{1,d}\left(y_1\left(t\right)\right)$ is modified as

$$f_{1,d,a,b}\left(y_1\left(t\right)\right) = \frac{\left(1 - e^{-\frac{\left(y_1(t)-a\right)^b}{l}}\right)}{d} \tag{6.1}$$

$\mathbf{y}\left(t\right) = \left(y_1\left(t\right), y_2\left(t\right)\right) \in \mathbb{R}^2$.

Here, the nonlinear models discussed in the previous chapter have been extended to suit the data-set of several drugs. Experimental data for various drugs is collected from the literature to examine the sustainability of the proposed models. The graphical illustrations and respective MSE values depict the robustness of nonlinear FDE models. The significance of the parameters and t-test on residuals is performed to test the validity of the presented models.

CHAPTER 7

Analysis of Fractional Multi-compartmental Pharmacokinetics Model with Metabolic Parameter and it's Application to F-choline

Nonlinear FDE system with the initial conditions for drug diffusion is considered as

$$D^{\alpha}\left[\mathbf{y}\left(t\right)\right]=f\left(t,\mathbf{y}\left(t\right)\right),\quad \mathbf{y}^{(m)}\left(t_{l}\right)=\mathbf{c}_{m},\ \ 0\leq m\leq\left[\alpha\right] \tag{7.1}$$

where $f:V\rightarrow\mathbb{R}^{4},\ V=[t_{l},\tau]\times\prod_{i=1}^{4}\left[y_{i}\left(t_{l}\right)-r_{i},y_{i}\left(t_{l}\right)+r_{i}\right],\quad \tau>t_{l}>0,\ r_{i}>0$ for $i=1,\cdots,4$ and $0<\alpha<1$.

Four-compartmental FDE to monitor F-choline activity in PET scan is proposed as

$$\begin{aligned}
D^{\alpha}y_{1}\left(t\right)&=-\left(k_{21}+k_{31}+k_{41}+k_{01}\right)y_{1}\left(t\right)+k_{12}y_{2}\left(t\right)+k_{13}y_{3}\left(t\right)+k_{14}y_{4}\left(t\right)\\
D^{\alpha}y_{2}\left(t\right)&=k_{21}y_{1}\left(t\right)-k_{12}y_{2}\left(t\right)-k_{02}f_{1}\left(y_{2}\left(t\right)\right)\\
D^{\alpha}y_{3}\left(t\right)&=k_{31}y_{1}\left(t\right)-k_{13}y_{3}\left(t\right)-k_{03}f_{2}\left(y_{3}\left(t\right)\right)\\
D^{\alpha}y_{4}\left(t\right)&=k_{41}y_{1}\left(t\right)-k_{14}y_{4}\left(t\right)
\end{aligned} \tag{7.2}$$

with initial conditions

$$y_{1}\left(0\right)=l,\ y_{2}\left(0\right)=0,\ y_{3}\left(0\right)=0,\ y_{4}\left(0\right)=0. \tag{7.3}$$

where $y_{1}\left(t\right),\ y_{2}\left(t\right),\ y_{3}\left(t\right)$ and $y_{4}\left(t\right)$ represents drug concentration in blood, kidney, liver and other tissues and organs respectively at time t. k_{ij} is the transfer rate from j^{th} to i^{th} compartment.

Model 1:

$$f_{1}\left(y_{2}\left(t\right)\right)=y_{2}\left(t\right)\quad\text{and}\quad f_{2}\left(y_{3}\left(t\right)\right)=y_{3}\left(t\right). \tag{7.4}$$

Model 2:

$$f_1\left(y_2\left(t\right)\right) = y_2\left(t\right) \quad \text{and} \quad f_2\left(y_3\left(t\right)\right) = \frac{y_3\left(t\right)}{K_{m_2} + y_3\left(t\right)} \tag{7.5}$$

and

Model 3:

$$f_1\left(y_2\left(t\right)\right) = \frac{y_2\left(t\right)}{K_{m_1} + y_2\left(t\right)} \quad \text{and} \quad f_2\left(y_3\left(t\right)\right) = \frac{y_3\left(t\right)}{K_{m_2} + y_3\left(t\right)} \tag{7.6}$$

where K_{m_1} and K_{m_2} are Michaelis–Menten parameters.

The study explores the application of fractional calculus over classical DE by considering four-compartmental linear and nonlinear fractional models. The existence, uniqueness, and stability of the system are discussed in either case. Comparison tests are applied, showcasing the potency of fractional over the classical approach. The statistical regression analysis has established relationships between drug concentration with parameters like transfer rates, elimination, metabolism rate, fractional order, etc.

CHAPTER 8

Summary and Conclusions

In chapter 3, the difference equation to calculate the concentration of drug in the bloodstream was derived in the study by identifying geometric series. It was solved and results were presented graphically to visualize the pattern and estimate the drug level. This model may be useful for recommending remedial actions to restore requisite drug level in cases of possible discrepancies occurring due to missing a dose or overdose. The half-life of the drug was considered as the factor of estimation. The differential equation approach was explored through zero-order and first-order equations to investigate continuous form of the pattern. The data fitting in the study revealed that, the first order kinetics demonstrated better results.

Multi-compartmental fractional models for drug absorption and disposition in PK/PD are solved using ADM, in chapter 4. Using analytic method ADM, a closed solution to non-commensurate FDE models is obtained in the study. Nonlinear regression is used for parameter estimation. Stability, existence and uniqueness for two-compartment model is exploited in the present study. The regression model is further validated statistically so that the mathematical model for drug diffusion in this context, forms a tool to comprehend the elements of bio-transport processes. Further ADM demonstrates its effectiveness in solving FDE, both linear and nonlinear, with reasonable computation and accuracy. In the concluding section, the authors illustrated through analytic model is robust than the previous literature stated by convolution form, assuring enhancement of drug delivery system.

Different linear and nonlinear models considering with and without metabolic

parameters to study the release profile of Diclofenac delayed release is explored in chapter 5. The existence and uniqueness of the suggested models have been discussed. The algorithm is presented to evaluate the considered models numerically and estimate the study parameters. Diclofenac concentration-vs-time graphs are plotted for various models, which are further compared w.r.t MSE. The t-test on residuals performed on the models validates the proposed models. The importance of the metabolism parameter is showcased in the continuous curves plotted. The existing linear models are now generalized to the nonlinear models in the present text.

In chapter 6, the validation process's outcomes show that the model can correctly forecast anomalous drug diffusion of delayed release concentrations, yielding significant understanding into the fundamental processes controlling drug release kinetics. The authors have considered a variety of anomalous drugs through which proposed models are supported. The verified models are an effective means for improving drug delivery systems and guaranteeing the production of more reliable and efficient pharmaceutical formulations, which have the potential to advance the field of pharmaceutical sciences significantly.

In chapter 7, the four-compartmental linear FDE model is proposed and analyzed. It has been further extended by considering metabolic parameters in the liver and kidney. Estimated parameters, along with a graphical representation of observed data points and continuous curves of concentration in the kidney and liver over time obtained by evaluating FDE, demonstrate the robustness of the models. The t-test on residuals, MSE calculated for all presented models, and comparison test prove the accuracy of the model's prediction ability. Thus, the study showcases the efficiency of fractional calculus over classical in pharmacokinetics.

In this study, we successfully developed and evaluated regression models for predicting drug concentration in anomalous environments. The results demonstrate the potential of proposed models in accurately predicting drug concentration, which can

inform the decision-making process. The estimated parameters of the model provide insights into the relationships between parameters and drug concentration. Our findings suggest that nonlinear fractional models outperformed linear classical models. Overall, this research contributes to developing predictive models for drug concentration in anomalous environments, which can have important implications (such as predictive toxicology, personalized medicine, dynamic monitoring etc) in pharmacokinetics.

CHAPTER 9

Future work

1. Implementing categorized and comparative study of various rates in drug diffusion.
2. Identifying and analyzing the models to predict drug-drug interaction.
3. Evaluating the non-commensurate models to interpret various processes in a human body.
4. Extending fractional calculus in the field of growth of tumor or cancer cells.

Publications

Journals:

1. Shilpa D'Cunha and V. R. Lakshmi Gorty, "Analysis of Non-commensurate Model of Diclofenac Concentration in the Plasma to Enhance Drug Delivery System", *Mathematical Modelling of Engineering Problems*, vol. 11, no. 6 , pp. 1428–1440, 2024. DOI https://doi.org/10.18280/mmep.110604. [ISSN:2369-0739; E-ISSN:2369-0747, Scopus indexed]

2. Shilpa D'Cunha and V. R. Lakshmi Gorty, "Nonlinear Models: Analysis of Anomalous Drug Diffusion", *Engineering Letters*, accepted, September 2024. [ISSN:1816-093X; E-ISSN:1816-0948, Scopus indexed, WoS]

3. Shilpa D'Cunha and V. R. Lakshmi Gorty, "Drug Level Modelling with Difference and Differential Equations", *Journal of Physics: Conference Series*, vol. 2287, no. 1, pp. 1-9, 2022. DOI 10.1088/1742-6596/2287/1/012011. [ISSN:1742-6588; E-ISSN:1742-6596, Scopus indexed]

4. Shilpa D'Cunha and V. R. Lakshmi Gorty, "Validating the Proposed Models for Anomalous Drug Diffusion in Delayed Release Concentrations", communicated.

5. Shilpa D'Cunha and V. R. Lakshmi Gorty, "Analysis of fractional multi-compartmental pharmacokinetics model with metabolic parameter with the application to F-choline", communicated.

Conferences:

1. Shilpa D'Cunha and V. R. Lakshmi Gorty, "Drug Level Modelling with Difference and Differential Equations" presented in the 12^{th} *International Conference on Applied Physics and Mathematics-ICAPM 2022*, 18-20 February 2022, Singapore.

2. Shilpa D'Cunha and V. R. Lakshmi Gorty, "Analysis of ADM solution for Non-commensurate Model in Anomalous Drug Diffusion" presented in the 4^{th} *International Conference on Materials, Manufacturing, and Modelling-ICMMM 2023*, 24-26 March 2023, VIT, Vellore, India.

References

[1] I. Podlubny, *Fractional differential equations: an introduction to fractional derivatives, fractional differential equations, to methods of their solution and some of their applications*. Elsevier, 1998.

[2] H. Jafari and V. Daftardar-Gejji, "Solving a system of nonlinear fractional differential equations using adomian decomposition," *Journal of Computational and Applied Mathematics*, vol. 196, no. 2, pp. 644–651, 2006.

[3] C. Ionescu, A. Lopes, D. Copot, J. T. Machado, and J. H. Bates, "The role of fractional calculus in modeling biological phenomena: A review," *Communications in Nonlinear Science and Numerical Simulation*, vol. 51, pp. 141–159, 2017.

[4] A. Rescigno, "Compartmental analysis and its manifold applications to pharmacokinetics," *The AAPS Journal*, vol. 12, no. 1, pp. 61–72, 2010.

[5] J. P. Lehoczky and D. P. Gaver, "A diffusion approximation analysis of a general n-compartment system[interim report]," 1976.

[6] A. Dokoumetzidis and P. Macheras, "Fractional kinetics in drug absorption and disposition processes," *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 36, pp. 165–178, 2009.

[7] J. K. Popović, M. T. Atanacković, A. S. Pilipović, M. R. Rapaić, S. Pilipović, and T. M. Atanacković, "A new approach to the compartmental analysis

in pharmacokinetics: fractional time evolution of diclofenac," *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 37, pp. 119–134, 2010.

[8] D. Verotta, "Fractional compartmental models and multi-term mittag–leffler response functions," *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 37, pp. 209–215, 2010.

[9] J. K. Popović, D. Dolićanin, M. R. Rapaić, S. L. Popović, S. Pilipović, and T. M. Atanacković, "A nonlinear two compartmental fractional derivative model," *European Journal of Drug Metabolism and Pharmacokinetics*, vol. 36, pp. 189–196, 2011.

[10] A. Dokoumetzidis, R. Magin, and P. Macheras, "Fractional kinetics in multi-compartmental systems," *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 37, pp. 507–524, 2010.

[11] D. Herceg, S. Ntouskas, P. Sopasakis, A. Dokoumetzidis, P. Macheras, H. Sarimveis, and P. Patrinos, "Modeling and administration scheduling of fractional-order pharmacokinetic systems," *IFAC-PapersOnLine*, vol. 50, no. 1, pp. 9742–9747, 2017.

[12] P. Sopasakis, H. Sarimveis, P. Macheras, and A. Dokoumetzidis, "Fractional calculus in pharmacokinetics," *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 45, pp. 107–125, 2018.

[13] K. Diethelm, N. J. Ford, and A. D. Freed, "Detailed error analysis for a fractional adams method," *Numerical Algorithms*, vol. 36, pp. 31–52, 2004.

[14] B. Bonilla, M. Rivero, and J. J. Trujillo, "On systems of linear fractional differential equations with constant coefficients," *Applied Mathematics and Computation*, vol. 187, no. 1, pp. 68–78, 2007.

[15] V. Lakshmikantham and A. S. Vatsala, "Basic theory of fractional differential equations," *Nonlinear Analysis: Theory, Methods & Applications*, vol. 69, no. 8, pp. 2677–2682, 2008.

[16] V. Daftardar-Gejji and H. Jafari, "Adomian decomposition: a tool for solving a system of fractional differential equations," *Journal of Mathematical Analysis and Applications*, vol. 301, no. 2, pp. 508–518, 2005.

[17] M. M. Hosseini and H. Nasabzadeh, "On the convergence of adomian decomposition method," *Applied Mathematics and Computation*, vol. 182, no. 1, pp. 536–543, 2006.

[18] K. Diethelm and A. D. Freed, "The fracpece subroutine for the numerical solution of differential equations of fractional order," *Forschung und Wissenschaftliches Rechnen*, vol. 1999, pp. 57–71, 1998.

[19] K. Diethelm, N. J. Ford, and A. D. Freed, "A predictor-corrector approach for the numerical solution of fractional differential equations," *Nonlinear Dynamics*, vol. 29, pp. 3–22, 2002.

[20] R. Garrappa, "On linear stability of predictor–corrector algorithms for fractional differential equations," *International Journal of Computer Mathematics*, vol. 87, no. 10, pp. 2281–2290, 2010.

[21] K. Thelen, K. Coboeken, S. Willmann, J. B. Dressman, and J. Lippert, "Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part ii: extension to describe performance of solid dosage forms," *Journal of Pharmaceutical Sciences*, vol. 101, no. 3, pp. 1267–1280, 2012.